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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,563	09/14/2001	Gerard Mathis	LOM 24	7143

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EXAMINER

MAUPIN, CHRISTINE L

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 03/27/2002

5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/936,563

Applicant(s)

MATHIS ET AL

Examiner

CHRISTINE L MAUPIN

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 September 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Sharon N. Thornton
SHARON N. THORNTON
PATENT ANALYST

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth as the subject matter which applicant(s) regard as their invention.

1. Method claims require a last step or phrase in the last step that states the accomplishment of the goals for the method that were stated in the method's preamble. Claims 1-19 lack such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted. The process of the claimed invention is a one step activity.

2. Regarding claims (1-19), the phrase "characterized in that" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "characterized in that"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d). This term is used throughout all the claims with the exception of claim 15, where "the method as claimed" is used referring to claim one. The appears to be a typing mistake in claim 15, but the use of the phrase

"characterized in that" renders it unclear of exactly what the Applicant is claiming, because the scope of the term may be either "comprising of" or "comprising". For examining purposes, it will be deemed equivalent to "comprising".

3. Claims 19 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 1-19 fails to correspond in a harmonization of nomenclature of which applicants regard as the invention can be found in searching for organic or inorganic terminology. In that paper, applicant has stated the Eu-cryptate is a macrocyclic complex and also a cryptate of many different ring or non-ring structure. These structures coordinated with the Eu can alternatively be named following organic definition or inorganic definitions. The complexes become indefinite and confusing when switching back and forth.

4. Claims 1, 2-4, and 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The last clause of the claim "said oligonucleotides comprising at least 5 phosphodiester-type internucleotide bonds at the end intended to be bonded" is unclear because it as to what the clause actually means in term of the chemistry or what is being formed and "phosphodiester-type internucleotide bonds" is indistinct and unspecific.

5. Claims 5 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such

omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: a functional group capable of bonding to a biological substance. This can be overcome by specifying the type of group such a carbonyl group or groups.

6. The term "(22)" in claim 11 is a relative term, which renders the claim indefinite. The term "(22)" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This may be a typing or translation error.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As defined in Academic Press in their Dictionary of Science and Technology a cryptate: is a complex molecule consisting of a central ion surrounded and shielded by a cyclic compound. In view of this definition the following rejections have been made concerning the Europium rare-earth cryptate as characterized in the Applicant's claims.

7. Claims 1-7, 9-11, 13, 15, 16, 17, 18, 19 rejected under 35 U.S.C. 102(b) as being anticipated by Li et al., (Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132.

8. Regarding claim 1 and 2, Li et al., (Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132.) teaches that a process for reduced quenching may be attained in a

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fluorescence assay characterized in that a fluorescent conjugate comprising and a oligonucleotides bonded to a Europium rare-earth metal cryptate is introduced into the medium (Li et al., *Bioconjugate Chemistry*, 1997, (8), Page 130, column 1, figure 1).

Europium lifetime is relative insensitive to environmental conditions and is less than 5 % for conjugation to single stranded or double stranded DNA (Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132., page 127, abstract, page 130 column 1, figure and figure paragraph, second paragraph titled "luminescence Measurements" and page 131, column 1).

9. Regarding claim 3 and 7, Li et al., (Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132.) Li et al., teaches a Europium rare-earth metal cryptate is bonded to a DNA introduced into the medium which has a phosphodiester-type bond, (abstract, also column 2 page 127, column 1 and 2 page 128, column, page 129 column1 second paragraph "conjugation to a 14 or 20 synthetic DNA oligomers.").

10. In claim 4, the process characterized in that the oligonucleotides consist of RNA of DNA units bonded to one another via phosphodiester bonds (column 1, page 128, figure 1).

11. Regarding claims 5 and 6, the process characterized in that oligonucleotides consist of RNA or DNA units, one of which may comprise a functional group introduced or generated on said unit, of the functional group introduced using a spacer arm bonded to the terminal phosphate group in the 5' or 3' position. Li et al., (Li et al., *Bioconjugate*

Chemistry, 1997, (8), p127-132.) Li et al., teaches a Europium rare-earth metal cryptate is bonded to a DNA introduced into the medium via a phosphodiester-type bond, by the 5' end of the amine modified DNA oligomer (abstract, also column 2 page 128, bottom of page, column 1 and 2 page 130, column, page 131 column 1 Specific reaction at 5' amine can be achieved without side reaction at the DNA bases")

12. Regarding claim 9, characterized in that the Europium rare-earth cryptate is bonded covalently to the oligonucleotides either directly or via a spacer arm is taught by (Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132., (abstract and page 127 column 2, and in figure 1 column 1, page 128).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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15. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132. in view of Hyldig-Nielson et al., U.S. Patent No. 5,985,563.

Li et al., teaches the limitations of claims 1-7, and 9 as discussed above.

Li et al., does not teach the use of PNA backbones.

Hyldig-Nielson et al., U.S. Patent No. 5,985,563 teaches PNA probes in detection of fluorescent assays.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Li et al. with the PNAs of Hyldig-Nielsen et al., U.S. Patent No. 5,985,563, (abstract, and column 1) because PNA probes form complexes with complementary nucleic acids which complexes are considerably more stable (higher T_m value) (Hyldig-Nielson et al., column 1 and 2) than would be a similar hybrid formed by a typical used nucleic acid probe of corresponding sequence allowing sensitive assays and hybridization with traditionally used nucleic acids probes is much faster in solution (column 2 lines 35-34). Hyldig-Nielson further state PNA probes and nucleic acids can be performed rapidly allowing greater flexibility in assay format, only slightly influenced by pH and salt concentration in the hybridization solution allowing PNAs to hybridize under conditions not favorable for ordinary DNA probes, and have a greater thermal instability of mismatching bases whereby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic probes of corresponding sequence would do (Hyldig-Nielson et al., column 1,

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lines 50-55). Hyldig-Nielson further state the structure of PNA is not degraded by nucleases or proteases making the PNA molecule very stable in biological solutions (column 1, lines 56-58).

16. Claims 10-13 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132, as applied to claims 1-,7 and 9 above, and further in view of Lehn et al., U.S. Patent No. 5,162,508, on November 10th 1992.

Li et al., teaches the limitations of claims 1-7, and 9 as discussed above.

Li et al., does not teach the method of making the rare-earth metal salt complex that the applicant is claiming, (Eu-cryptate or Eu[Bisdiethoxybipyridine.bipyridine].

Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992, teaches the use of Eu rare-earth cryptates as tracers or biological probe in biological assays.

Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992, teaches the use of Eu rare-earth cryptates as tracers or biological probe specifically in DNA and RNA (Column 20, lines 1- 20).

Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992 does specifically teach the construction or the length of the spacing arm or that polynucleic acid were incorporated as part of the used in biological assays, and that the total flourscence of the rare-earth Eu cryptate is dependent upon.

17. Claims 10-13, and 15-19, are characterized in that the said Europium rare-earth cryptate consist of at least one rare-earth metal salt complex with a macropolycyclic compound of the formula (I, II and III) are taught by Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992. (Columns 1-8) resulting in the same complex that the applicant is claiming, (Eu-cryptate or Eu[Bisdiethoxybipyridine.bipyridine], (Column 11 and 12) in the instant application.

18. Claim 10, (A), (B), (C), are taught by Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992. (A), (B), and (C) are independently of each other, hydrocarbon-based chains which optionally contain one or more hetero atoms and are optionally interrupted with a hetero macrocycle, at least one of the radicals (A), (B), (C),, also comprising at least one molecular unit or consisting essentially of a molecular unit, said molecular unit having triplet energy which is greater than that of the emission level of the complexed rare-earth metal ion.(column 1 lines 24-65).

19. Claim 11, Lehn et al. further teaches the macrocyclic or macropolycyclic compounds, U.S. Patent No. 5,162,508 on November 10th 1992. (Column, 10-19).

20. Regarding Claim 12 and 13 (R), (R'), (Y), (Z), are taught by Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992. Where R is a methyl group or represents the group – Y-Z. (Lehn et al., U.S. Patent No. 5,162,508 column 3, lines 43 and 44). Where R' is a hydrogen or a group –COOR'', in which R'' is a C₁ to C₁₀ alkyl group and

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preferably represents the methyl, ethyl, or tert-butyl group, or alternatively R' is a group CO-NH-Y-Z. (Lehn et al., U.S. Patent No. 5,162,508 column 3, lines 45-49). Where Y is a spacer arm or group which consist of divalent organic radical selected from linear or branched C₁ to C₂₀ alkylene groups optionally containing one or more double bonds and/or optionally being interrupted by one or more heteroatoms such as oxygen, nitrogen, sulfur or phosphorus, or from C₅ to C₈ cycloalkylene, cycloalkylene or arylene groups, the said alkylene, cycloalkylene or arylene groups optionally being substituted by alkyl, aryl, or sulfonate groups. (Lehn et al., U.S. Patent No. 5,162,508 column 3, lines 31-40). Where Z is a functional group capable of bonding covalently with a biological substance. (Lehn et al., U.S. Patent No. 5,162,508 column 3, lines 41 and 42). Regarding claim 12 and 13, Lehn et al. teaches further that the length of the spacing arm may be up vary up to 20 atoms and contain oxygen, nitrogen, sulfur or phosphorus. (Lehn et al., U.S. Patent No. 5,162,508 column 1, lines 60-65). Where Y is a spacer arm or group which consist of divalent organic radical selected from linear or branched C₁ to C₂₀ alkylene groups optionally containing one or more double bonds and/or optionally being interrupted by one or more heteroatoms such as oxygen, nitrogen, sulfur or phosphorus, or from C₅ to C₈ cycloalkylene, cycloalkylene or arylene groups, the said alkylene, cycloalkylene or arylene groups optionally being substituted by alkyl, aryl, or sulfonate groups. (Lehn et al., U.S. Patent No. 5,162,508 column 3, lines 31-40).

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21. Regarding claims 15 and 16, where complex that the applicant is claiming, (Eu-cryptate or Eu[Bisdiethoxybipyridine.bipyridine], are taught by Lehn et al., U.S. Patent No. 5,162,508 on November 10th 1992. (Columns 9 and 10) and (Column 24, line 56).

22. Regarding claim 18, characterized in that the fluorescent Europium conjugate is bonded covalently to one of the members of a pair of molecules capable of binding specifically to one another, in particular a cellular receptor, an antigen, an antibody or nucleic acid. Lehn et al. teaches that a process comprising a rare earth cryptate bonded covalently to a biological substance via a spacing arm to be assayed or detected by fluorescence. (Column 1, lines 40-70) and (Column 19, line 54) Lehn et al., also teaches that the covalent bonding may be via a linkage with phosphorus (Column 1 and 2). Lehn et al., U.S. Patent No. 5,162,508 also teaches in Experiment B that the Eu rare-earth cryptate may be covalently bonded to a monoclonal antibody (Column, 20-22, all text), which is made of nucleic acids. (Columns 20-23, all text).

23. Regarding claim 19, characterized in that, in addition to said fluorescent Europium rare-earth conjugate, a fluorescent label comprising and acceptor fluorescent compound in the assay. Li et al., *Bioconjugate Chemistry*, 1997, (8), p127-132.

Li et al., teaches the process of a using Europium rare-earth conjugate as a fluorescent label comprising and acceptor fluorescent compound in the assay fluorescent and discusses the differences in lifetimes. Li et al., *Bioconjugate Chemistry*, 1997, (8), (see page132, Energy Transfer).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Li et al. with the method of Lehn et al. Lehn et al., U.S. Patent No. 5,162,508, (Abstract and Column 23 lines 15-25). Because the use of Eu rare-earth cryptates as tracers or biological probe in biological assays is particularly advantageous by comparison with the assays processes using a radioactive element, which requires a much longer incubation time, washing steps and handling of a radioactive element, the combination of Eu rare-earth cryptates to functional group capable of bonding covalently with a biological substance can be advantageous carried out in conventional processes with organic solvent by those that are well known to those skilled in the art. (Lehn et al., U.S. Patent No. 5,162,508, (Abstract and Column 23). Lehn et al., U.S. Patent No. 5,162,508, teaches that the fluorescent Europium conjugate is bonded covalently to one of the members of a pair of molecules capable of binding specifically to one another, in particular a cellular receptor, an antigen, an antibody or nucleic acid. Lehn et al. teaches that a process comprising a rare earth cryptate bonded covalently to a biological substance via a spacing arm to be assayed or detected by fluorescence. (Column 1 and 2 lines) and (Column 19, line 54). Lehn et al., also teaches that the covalent bonding may be via a linkage with phosphorus (Column 1 and 2). Lehn et al., U.S. Patent No. 5,162,508 also teaches in Experiment B that the Eu rare-earth cryptate may be covalently bonded to a monoclonal antibody (Column, 20-22, all text), which is made of nucleic acids. (Columns 20-23, all text). One skilled in the art may further reasonably anticipate that and the spacer arm may be replaced with oligonucleotides and that different spacer arms with different

lengths and construction will result in different rate of quenching or completely stop any quenching process.

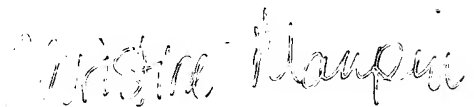
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine L. Maupin whose telephone number is 703-308-3617. The examiner can normally be reached on 9:00am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.


JEFFREY FREDMAN
PRIMARY EXAMINER



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Christine L. Maupin
Examiner
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